REMARKS

I. Status Summary

Claims 32 and 33 are pending in the subject application.

Claims 32 and 33 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "highly conserved antigen" is indefinite.

Claims 32 and 33 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Engel *et al.* (3 Immunity 39-50, 1995; hereinafter "Engel") in view of Sato *et al.* (15 J Immunol 4371-8, 1996; hereinafter "Sato") and Nielsen *et al.* (2 EMBO J 115-19, 1983; hereinafter "Nielsen").

II. Response to the Rejection under § 112, Second Paragraph

Claims 32 and 33 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "highly conserved antigen" is indefinite. According to the United States Patent and Trademark Office (hereinafter "the Patent Office"), the specification fails to define the term, and does not provide a standard for ascertaining the requisite degree with respect to what antigen is considered as highly conserved.

After careful consideration of the rejection and the Patent Office's basis therefor, applicant respectfully traverses the rejection and submit the following remarks.

Initially, applicant respectfully submits that the phrase "highly conserved antigen" initially appeared in the claims with the addition of claim 32 in Amendment D, dated August 13, 2003. Applicant respectfully submits that claim 32 was allowed in an Official Action dated November 6, 2003, and allowance of this claim was confirmed in an Advisory Action dated March 24, 2004. Applicant respectfully submits that claim 32 has not been amended since it appeared in Amendment D in such a way as to impart any ambiguity into the now objected to phrase, and as such, submit that the instant rejection is improper.

Furthermore, applicant respectfully submits that the phrase "highly conserved antigen" is discussed extensively in the specification of the instant application, including particularly at page 4, lines 21-29, page 10, lines 8-20, page 14, lines 11-21, and page 38, lines 9-17. In each of these cases, a highly conserved antigen is described as being

one that a vertebrate (for example a mammal such as a mouse or a human) would ordinarily not be able to mount an immune response against due to the antigen being seen by the vertebrate's immune system as "self". Applicant respectfully submits that this usage is consistent with the skilled artisan's understanding of the term "highly conserved antigen". Given the requirement that the terms of a claim are to be interpreted from the perspective of the skilled artisan, applicant respectfully submits that the claim term is not ambiguous as asserted by the Patent Office, and thus clearly defines the metes and bounds of the claim.

Accordingly, applicant respectfully submits that the phrase "highly conserved antigen" is understood by the skilled artisan, and that as a result, the metes and bounds of the claims are clear. Thus, applicant respectfully requests that the rejection of claims 32 and 33 under 35 U.S.C. § 112, second paragraph, be withdrawn, and the claims allowed at this time. Applicant respectfully solicits a Notice of Allowance to that effect.

III. Response to the Rejection under § 103(a)

Claims 32 and 33 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Engel in view of Sato and Nielsen. According to the Patent Office, Engel teaches immunizing CD19 transgenic mice overexpressing CD19 with an antigen (DNP-KLH), that hCD19 transgenic mice had an overall increase in serum immunoglobulin levels, and that overexpression of CD19 appears to render B cells more susceptible to differentiation induction. The data in Table 2 are asserted to show that the levels of isotype IgG2a and IgG2b antibodies are particularly higher in the hCD19 transgenic mice compared to wild type controls. The Patent Office concedes, however, that Engel does not teach that hCD19 transgenic mice could be used for production of autoantibodies.

According to the Patent Office, this deficiency is cured by Sato and Nielsen. The Patent Office asserts that Sato supplements the teachings of Engel by disclosing a correlation between the increased expression of CD19 with increased levels of endogenous autoantibodies, and that CD19 serves as a cell surface response regulator that establishes signaling thresholds critical for B lymphocyte development and

activation, particularly the proliferation of $CD5^+$ B-1 cells that are known to be associated with the production of autoantibodies and autoimmune disease. The Patent Office further asserts that Sato teaches that increased CD19 expression may lead to heightened responsiveness to weak antigens (which the Patent Office equates with "highly conserved antigens"). The Patent Office concedes that Sato does not use an autoantigen to immunize CD19 transgenic mice, but nonetheless contends that Sato suggests to the skilled artisan that CD19 transgenic mice could be used for the production of autoantibodies.

The Patent Office concedes that Engel and Sato do not teach the production of monoclonal antibodies recited in steps (b) through (e) of claim 32 or specific affinity constants for the monoclonal antibodies produced. According to the Patent Office, this defect is cured by Nielsen. Nielsen is asserted to teach a method of making monoclonal antibodies via hybridoma formation similar to that claimed in steps (b) through (e) of claim 32, which can be used to obtain antibodies having an affinity constant greater than 1×10^5 L/mol.

Thus, the Patent Office asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Engel, Sato, and Nielsen to arrive at the instant invention. The Patent Office asserts that the motivation to do so because it is a practical means for obtaining autoantibodies, which are useful in many diagnostic procedures.

After careful consideration of the rejection and the Patent Office's bases therefor, applicant respectfully traverses the rejection and submit the following remarks.

Initially, applicant respectfully submits that the Patent Office has chosen isolated passages from Engel in order to support the asserted combination, and that when read as a whole and in context, Engel teaches away from the use of CD19 transgenic mice as sources of antibody-producing cells for the production of hybridomas. For example, Engel teaches that the development of immature and mature B cells in the bone marrow of CD19 transgenic mice is severely impaired. See Engel at page 40. Furthermore, Engel teaches that in CD19 transgenic mice, immature B cells (IgM^+ $B220^{lo}$) were significantly reduced in the bone marrow, as were B cell numbers in the blood (95%

decrease), spleen (82% decrease), and peritoneum (70% decrease). Applicant respectfully submits that given the abnormal B cell development observed in CD19 transgenic mice, particularly the lower B cell numbers in the spleen, one of ordinary skill in the art would not have been motivated to produce hybridomas using spleen cells isolated from CD19 transgenic mice. Thus, it is believed that there is no basis or motivation to combine Engel with Sato and Nielsen as proposed by the Patent Office.

Applicant further submits that the skilled artisan would not be motivated to use CD19 transgenic mice based on the Engel reference for another reason. Engel teaches that CD19 is involved in transmembrane signaling related to negative selection and clonal deletion of immature B cells in the bone marrow. According to Engel:

> The finding that overexpression of CD19 results in increased sensitivity to transmembrane signals in combination with the finding that overexpression of CD19 results in clonal elimination of B cells in the bone marrow suggests that CD19 regulates antigen-dependent negative selection of immature B cells during maturation in the bone marrow. Since impaired B cell development in hCD19TG mice is directly correlated with the number of cell surface hCD19 molecules expressed...increased receptor number may translate into the overproduction of intracellular signals, which exceeds the signaling threshold and results in down-regulation of immature B cell development. Since many preimmune B cells produce self-reactive antibodies...lowering the surface immunoglobulin signaling threshold for negative selection by overexpressing CD19 may explain the severe deficiency of B cells in hCD19TG mice...Thus, overexpression of CD19 may augment transmembrane signals generated through low affinity antigen receptors, thereby leading to increased clonal deletion of immature B cells in the bone marrow.

See Engel at page 47 (emphasis added). As described in more detail in Engel, overexpression of CD19 leads to increased sensitivity to transmembrane signaling concomitant with increased antigen-dependent negative selection of immature B cells.

Increased clonal deletion and/or negative selection would be expected to result in a decrease in both the antigen-binding affinities and antigen-binding repertoire of the antibody-producing cells (and hence the antibodies produced by these cells) present in CD19 transgenic mice under conditions of augmented transmembrane signaling for at least two reasons. First, high affinity antibodies are more likely to be clonally deleted;

and second, increased transmembrane signaling driven by CD19 overexpression would lead to the clonal deletion of antibody-producing cells that would not have been deleted in the absence of CD19 overexpression. Increased clonal deletion would result in a reduction in the numbers of B cells exiting the bone marrow (Engel specifically teaches that B cell numbers in the CD19 transgenic mice were drastically reduced both in tissues and in the blood). Therefore, the antigen-binding repertoire of CD19 transgenic mice would be expected to be reduced as compared to that seen in a wild-type mouse.

As a result, applicant respectfully submits that one of ordinary skill in the art would expect the hybridomas produced using CD19 transgenic antibody-producing cells to produce a limited repertoire of low affinity antibodies, a fact that would strongly discourage the skilled artisan from employing these mice as sources of antibody-producing cells for the production of hybridomas. Given the time and expense required to produce monoclonal antibodies, applicant respectfully submits that one of skill would not begin this process if the likely result would be the production of low affinity monoclonal antibodies with a limited antigen-binding repertoire.

Accordingly, applicant respectfully submits that the skilled artisan would understand Engel to teach that the CD19 transgenic mice are characterized by significant defects in B cell development and maturation, and that these defects would have a drastically negative impact on the usefulness of these mice in the production of monoclonal antibodies. As such, applicant respectfully submits that the motivation to use CD19 transgenic mice for producing monoclonal antibodies cannot be found in Engel, and further that Engel actually teaches away from making monoclonal antibodies from CD19 transgenic mice. Thus, it is believed that there is no basis or motivation to combine Engel with Sato and Nielsen as proposed by the Patent Office.

The deficiencies of Engel as part of the cited combination are not cured by Sato. The Patent Office asserts that Sato supplements the teachings of Engel by disclosing a correlation between increased CD19 expression and increased levels of endogenous autoantibodies. According to the Patent Office, Sato teaches that CD19 serves as a cell surface response regulator that establishes signaling thresholds critical for B lymphocyte development and activation, particularly the proliferation of $CD5^+$ B-1 cells,

which are known to be associated with the production of autoantibodies and autoimmune disease. However, applicant respectfully submits that Sato itself clearly states that "this study does not demonstrate that $CD5^+$ B cells are responsible for the production of autoantibodies" (Sato at page 4377). Thus, the Sato reference itself refutes the Patent Office's assertion that CD19 influences $CD5^+$ B-1 cell development and that this is relevant to the production of autoantibodies generally.

Furthermore, applicants respectfully submit that the disclosure of Sato is insufficient to overcome the teaching away from using CD19 transgenic mice for the production of monoclonal antibodies found in the Engel reference. As stated above, Engel discloses that B cell numbers were significantly decreased in the blood (95% decrease), spleen (82% decrease), and peritoneum (70% decrease) of CD19 transgenic mice. Given that the spleen is the source of cells for monoclonal antibody production, one of ordinary skill in the art would not be motivated to use an animal in which antibody-producing cells are decreased by more than 80%. Thus, even if $CD5^+$ B cells increased in numbers and proportions as asserted by the Patent Office, since Sato explicitly states that "this study does not demonstrate that $CD5^+$ B cells are responsible for the production of autoantibodies", applicant respectfully submits that Sato does not disclose or suggest an increase in a cell type that is relevant to the production of monoclonal antibodies to highly conserved antigens or to autoantigens. Rather, applicant respectfully submits that only by piecing together isolated passages of Engel and Sato combined with hindsight vision of applicant's instant specification can the Patent Office combine Sato and Engel to arrive at the instantly claimed subject matter with a reasonable expectation of success. As this is an inappropriate basis for a rejection under 35 U.S.C. § 103, applicant respectfully requests that the instant rejection be withdrawn at this time.

And finally, even if the teachings of Sato are viewed in isolation as would be required to support the Patent Office's contentions, applicant respectfully submits that at best Sato provides a mere invitation to experiment that does not result in a reasonable expectation of success in creating monoclonal antibodies from CD19 transgenic mice. As such, applicant respectfully submits that the Patent Office's basis for the instant

rejection is simply that it would be within the skill of the ordinary artisan to create monoclonal antibodies from CD19 transgenic mice. However, as stated in M.P.E.P. § 2143.01, this is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references, and applicant respectfully submits that such an objective reason cannot be found to make the proposed combination since the Engel reference specifically teaches away from the instantly claimed subject matter.

And finally, Nielsen is cited for its teachings of a general method of monoclonal antibody production, and thus does not overcome the combined deficiencies of Engel and Sato regarding the use of CD19 transgenic mice for monoclonal antibody production.

Accordingly, applicant respectfully submits that the cited combination does not support a *prima facie* case of obviousness. Applicant respectfully requests that the rejection of claims 32 and 33 under 35 U.S.C. § 103(a) over Engel in view of Sato and Nielsen be withdrawn, and the claims allowed at this time.

CONCLUSIONS

In light of the above remarks, applicant submits that the subject patent application is in condition for allowance and such allowance is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to place the application in condition for allowance.

Application No.: 09/555,349

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 12/02/2004 By: _____

Arles A. Taylor, Jr.
Reg. No. 39,395

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